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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/524,454	03/10/2000	Kristian Berg	697.013US1	5804

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EXAMINER	
EWOLDT, GERALD R	
ART UNIT	**PAPER NUMBER**
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/524,454	BERG ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *2,4,8-10 and 24-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,4,8-18,24-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed 11/02/07 in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's amendment, remarks, and IDS filed 11/02/07 have been entered.

2. Claims 2, 4, 8-10, 24-34, and newly added Claims 35 and 36 are pending and being acted being acted upon.

3. Upon reconsideration the previous rejection under the first paragraph of 35 U.S.C. § 112 for the introduction of new matter into the claims has been withdrawn.

4. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 2, 4, 8-10, 24-34, and newly added Claims 35 and 36 stand/are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the specification provides insufficient evidence that the claimed method could be used for expressing a molecule on a cell, said method comprising photochemical internalization wherein the molecule is sufficient to generate an immune response (Claim 24), more specifically CTL mediated cell killing (Claim 2), for the reasons of record.

As set forth previously, the breadth of the claims, in light of the limited disclosure of the specification, would not allow one of skill in the art to practice the invention as broadly claimed without an undue amount of experimentation.

First note that it is clear that the photochemical method (employing certain disclosed agents) of the instant application (and the prior art) can be used to internalize exogenous molecules. The method of the instant claims, however, requires more. The claimed method requires the surface presentation of a sufficient amount of the internalized molecule to generate an immune response.

It is well-known in the immunological arts that only certain antigen presenting cells are capable of presenting antigens and generating an immune response. See, for example, Janeway et al. (1994) wherein it is taught that in addition to antigen presentation, costimulation that can only be provided by B cells, macrophages, or dendritic cells, is required for the generation of an immune response. Accordingly, it appears that the method of Claims 2-5 and 7-11, employing any cell capable of photochemical internalization, could not be performed without an undue amount of experimentation.

Further regarding the breadth of the claims, the specification discloses only the actual use of $AlPcS_{2a}$ and $TPPS_{2a}$ as photochemical internalization agents. Claims 2-7 and 9-11 comprise either no limitations regarding photochemical internalization agents, or as in the case of Claim 7, are drawn to whole classes of agents. The disclosure of two related species of agents cannot be considered to be reasonably sufficient to enable the method of the instant claims to be performed with any of the essentially unlimited number of disclosed families of chemicals without an undue amount of experimentation.

Finally, it remains the Examiner's position that the disclosure of the specification does not sufficiently demonstrate the required limitation that the claimed method be capable of inducing sufficient MHC class I presentation of an antigen to generate an immune response. As set forth previously, the specification fails to disclose any actual Class I MHC presentation. Indeed, the only experiment which might demonstrate any sort of surface presentation, Example 3, clearly demonstrates the opposite, the triangles of Figure 4 show a *lack* of antigen on the surface of the cells.

Applicant's arguments, filed 11/02/07 have been fully considered but they are not persuasive. Applicant again cites Example 2.

Example 2 was discussed in the Office action of 1/09/07. Regarding Example 2, said example was discussed in the actions of 4/01/05 and 11/29/05:

In regards to Example 2, the methods of the example are not the methods of the instant claims, nor are they representative of the scope of the methods of the instant claims. In the example, a single cell type is loaded with a particular antigen; said loaded cell is then used in a CTL ^{51}Cr release assay. The CTLs employed in a ^{51}Cr assay are primed/activated CTLs and are not representative of the generation or stimulation of an immune response, i.e., the method of the instant claims See, for example, Janeway et al. (1994) wherein one of the fundamental rules of cellular immunology is taught, i.e., that the generation of an immune response from naïve T cells *requires* professional APCs. Clearly then, the ^{51}Cr assay of Example 2 employs primed/activated CTLs and does not comprise the generation or stimulation of an immune response. Note also that the specification discloses that the assay of Example 2 is the assay of Fossum et al. (1995) in which primed CTLs were employed. Accordingly, it remains the Examiner's position that given the breadth of the claimed method, i.e., the employment of *any*

cell type in the production of cells capable of generating an immune response (in defiance of one of the fundamental concepts of cellular immunology), the specification provides insufficient support and is not enabling.

Further, because the example comprises no appropriate controls, the skilled artisan would know that no conclusions could be drawn based on the disclosed results. Regarding Claim 6, first note that the limitations of the claim apply only to Claim 6, regardless, neither all types of lymphocytes nor all types of cancer cells are capable of the stimulation/generation of any/all types immune responses as are encompassed by the instant claims.

Also note that the example is not representative of the generation of cytotoxic T cell killing which encompasses the generation of activated T cells from naïve T cells.

Regarding Applicant's argument that the Examiner has found the example to be enabled, it is noted that there are no claims pending limited to the scope of the example.

Applicant cites pages 8-10 of the specification.

It is unclear how the disclosure of these pages enables the claimed method. The bulk of the cite merely describes the function of antigen presenting cells.

Applicant argues that the Examiner has failed to recognize the "compelling evidence of enablement" provided by Applicant.

Applicant's evidence has not been found to be compelling for the reasons of record.

Applicant states that the Inventor's declaration was not filed as a source of missing information but rather as evidence that the results are not unpredictable.

Applicant's reasons for filing the Inventor's declaration are noted, said reasons, however, do not change the teachings of the declaration that the specification is deficient.

As set forth previously, said declaration was considered in the Office action of 2/10/03:

In regards to the 1.132. declaration of Inventor Hogset, it is now disclosed that factors not disclosed in the specification are critical to the functionality of the claimed method. "Whether or not cell death results after photochemical treatment is principally dependent on two factors. Firstly the amount of toxic substances generated by the photosensitizing compounds on exposure to light and secondly, the presence and toxicity of molecules which are internalized during this process." Again, given the lack of guidance in the

specification, the claimed method must then be considered highly unpredictable and requiring of undue experimentation in view of these newly disclosed factors.

Regarding the photosensitizing compounds and exposure to light, while specific photosensitizing compounds are disclosed and claimed, no specific concentrations of said photosensitizing compounds (other than that used in Example 2) are claimed nor disclosed. Clearly, this parameter must be considered in that too much photosensitizing agent will induce cell death. Even more importantly, the declaration discloses that, whereas "the level of toxic substances which are generated may be controlled by the selection of the photosensitizer to be used, [and] the dose of that photosensitizer, but most crucially, the time of illumination which leads to increasing levels of the toxic substances" [must be considered]. The declaration goes on to demonstrate that too little light will not induce internalization while too much light kills the cells. Again it is clear, particularly in regards to the light parameters, i.e., source (wavelength), intensity, and duration, that the specification provides insufficient support for the claimed method. Again, given the lack of guidance in the specification, the claimed method must then be considered highly unpredictable and requiring of undue experimentation.

Finally, regarding the antigen to be internalized, the instant declaration states "the toxicity resulting from the molecules which are introduced may be readily controlled by selecting an appropriate toxic or non-toxic molecule for transfer, depending on the desired end use." The specification discloses however, that essentially any antigen can be used including "all manner" of pathogenic antigens, as well as peptides involved in diseases ranging from cancer to multiple sclerosis. The specification fails, however, to disclose how to "appropriately select" among the toxic and non-toxic molecules. Indeed, even the instant post-filing declaration fails to indicate how such a selection is to be made; it only indicates that said selection is essential, which once again demonstrates the lack of guidance in the specification.

Regarding toxicity, the specification fails to even mention this possible problem. Said problem was brought to light only in the Inventor's own post-filing declaration. Clearly then, the specification cannot be enabling in this regard.

Applicant alleges that the relevance of Example 2 has been dismissed by the Examiner.

Applicant's allegation is clearly not true as the Example has been considered and addressed multiple times. The Example has not been found enabling for the breadth of the claimed method as set forth above.

Applicant argues that the generation of primed CTLs is not necessary, submitting Salgaller et al. (1996) in support.

The teachings of Salgaller et al. are not in the scope of the method of the instant claims. Salgaller et al. preselected specific peptides from a well-known and previously characterized

tumor associated antigen (gp100) based on recognition in culture by tumor infiltrating lymphocytes. Note that only responding cultures are discussed, i.e., there is no discussion of how many cultures failed to respond to stimulation. Contrast this to the method of the instant claims which simply recite a method of inducing CTLs or a generic immune response to any peptide under any, including *in vivo*, conditions. Accordingly, the reference cannot provide support for the broad method of the instant claims.

Applicant cites Valmori et al. (1998) as teaching the generation of primed CTLs.

None of the instant claims recite any method steps for the priming of CTLs. Accordingly, it is unclear how the reference supports the claimed method.

Applicant argues that cancer vaccines are known in the art. And that down regulation of MHC Class I is not a universal phenomenon.

Applicant's argument is noted, but the fact remains that the instant specification fails to address the issue of down regulation of MHC Class I by some tumors.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 2, 4, 8-10, 24-34, and newly added Claims 35 and 36 stand/are rejected under 35 U.S.C. 102(b) as being anticipated by WO 96/07432 (IDS).

As set forth previously, WO96/07432 teaches a method of expressing [now presenting an antigenic molecule on the surface of a viable cancer cell, said method comprising:

contacting said cell *in vitro* [and *ex vivo*] with said antigenic molecule [now peptide] (including a vaccine component, a molecule capable of stimulating an immune response, and a peptide, also including an antigen bound to a carrier molecule) and with a photosensitizing agent (a porphyrin, phthalocyanine, purpurin, chlorin, benzoporphyrin, naphthalocyanine, cationic dye, and tetracycline, including $TPPS_4$, $TPPS_{2a}$, and $AlPcS_{2a}$, also including a

photosensitizing agent bound to a carrier molecule), wherein said molecule and said agent are each taken up into an intracellular membrane-restricted compartment of said cell; and irradiating said cell with light of a wavelength effective to activate the photosensitizing agent, such that the membrane of said intracellular compartment is disrupted, releasing said molecule into the cytosol of the cell, without killing the cell by irradiation, wherein, said released antigenic molecule, or a part thereof of sufficient size to generate an immune response, is subsequently presented on the surface of said cell by a class I MHC molecule (see particularly the claims). Note that reference does not specifically state that the method results in the cell surface expression of the antigen in MHC Class I, however, the reference teaches the same steps as those of the instant claims, thus, said same steps would inherently result in the same outcome, i.e., the claimed method of the expressing an antigenic molecule on the surface of a viable cell.

Applicant's arguments, filed 11/02/07 have been fully considered but they are not persuasive. Applicant argues that the claimed method is directed to a method of presenting an *antigenic peptide* on the *surface* of a *viable* cancer cell or antigen presenting cell whereas the method of the prior art is limited to delivery *of active, whole molecules* to the *cytosol* of cells. Applicant then discusses the Examples in detail.

While Applicant cites the Examples, the reference further teaches the delivery of peptides (Claim 2) which would be antigenic depending on the context, *in vivo* (page 6). Further note that essentially all of the cells described and used in the reference are cancer cells. The result of the delivery of peptides *in vivo* by the identical methods would necessarily be the same result achieved by method of the instant claims.

8. The following are new grounds for rejection necessitated by Applicant's amendment.

9. Claims 35 and 36 are rejected under 35 U.S.C. 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically, a method employing a peptide of 8 to 75 amino acids.

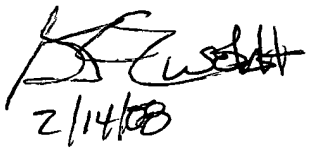
Applicant cites page 7 and Example 2 of the specification in support for these agents.

A review of the specification fails to show a genus of peptides of the recited length.

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara, Ph.D. can be reached on (571) 272-0878.

12. **Please Note**: Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197.



2/14/08

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